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DUCTAL CARCINOMA IN SITU OF THE FEMALE BREAST

Dr. Elgaili Mohamed, Prof A.A. Mohammadani, Dr. Mukhtar Elkhatim.

Panoramic View:

The breast is the most common site of cancer in females in many parts of the world. Mammary carcinoma is either ductal arising from ducts or lobular arising from lobules. When ductal carcinoma is still confined to the mother duct it is called ductal carcinoma in situ "DCIS" & when confined to the lobules it is called lobular carcinoma in situ "LCIS".

Historical Review:

Comedo carcinoma was the first type of DCIS identified in 1893. Bloodgood wrote "I assisted Dr. Halsted in exploring a clinically benign tumour of the breast. The moment we cut into & pressed on it, there exuded from its surface many greyish white granular cylinders which I called at that time comedos. From the gross appearance, the tumour was diagnosed as malignant and the radical operation was performed. The nodes were not involved[1].

Micrographs of other forms of what we would now call DCIS appeared in the literature in the 1900s. These included papillary, micropapillary and cribriform carcinomas that formed palpable masses judged to be malignant on gross examination [2].

In 1911, William McCarty raised on a genius question by asking: Is it necessary to wait for the penetration of the basement membrane before making a diagnosis of carcinoma? [3]. In 1913, he published a paper that illustrated the cytological differences between normal cells & those of invasive carcinoma. He illustrated comedocarcinoma & convincingly demonstrated that the abnormal cells in the ducts were cytologically identical to those of the invasive carcinoma [4].

In all editions of Ewing's book "Neoplastic Diseases"[5], first published in 1919, he illustrated a case of lobular carcinoma in situ "LCIS" and referred to is as precancerous. In the subsequent editions, he illustrated two photomicrographs of DCIS, one is a cribriform/micropapillary & the other is a comedocarcinoma. In his final 4th edition, in 1940, he explained that these tumours grow in distended ducts over considerable segments of the breast. Such tumours are slow to involve the lymph nodes but eventually they break through the basement membrane & infiltrate the fat & connective tissue in the form of alveolar carcinoma, his term for infiltrating ductal carcinoma.

The term cribriform carcinoma was well established by 1933 when Schultz-Brauns [2] illustrated the sieve-like type of cribriform DCIS by a drawing as well as a photograph.

The concept of preinvasive carcinoma of the human breast was firmly established in the United Kingdom by the early 1930s. In 1933, the pathologist Dawson [6] concluded that carcinoma always arose in ducts and "in the majority of cases in the terminal intralobular ducts". She also recongnised cancerisation of the individual lobular ductules concluding that "involvement of the lobules is not primary but secondary, and is evidence of extension of the cancerous process". Her major conclusions are based on meticulous review of normal and abnormal breast.

In 1932, Brooders [7], coined the phrase carcinoma in situ. He demonstrated examples of five organs, one of which was a breast lobule that he called "Adenocarcinoma in situ". His photograph is an indubitable example of what became known in 1941 as lobular carcinoma in situ [8, 9].

In 1935, Muir, a Scottish pathologist might have been the first to use the term intraduct carcinoma. He noted that proliferating ductal epithelial cells have acquired the essential characters of malignant neoplasia and they acquire this character before they transgress the normal boundaries [8].

In 1934 Foote and Stewart, pathologists at the Memorial Hospital for Cancer and Allied Diseases, wrote papers covering benign and malignant conditions of the breast [9, 10]. In one paper, they illustrated a lesion diagnosed as "non infiltrating papillary carcinoma" that is cytologically and architecturally identical to their illustration of an infiltrating papillary carcinoma. They observed that the individual cells are usually of medium size and they do not vary a great deal in configuration and stainability. Hyperchromatism is not

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impressive and the rate of cell division is low". Using today's terminology, their intraductal carcinoma is a cribriform DCIS and the infiltrating lesion is an infiltrative cribriform carcinoma. The difficulty of diagnosing intraductal lesions is evident in their statements "there is a zone of altered cell growth where the diagnosis of carcinoma versus atypical papillomatosis is a question of occult distinction and must be accepted or rejected on grounds of faith in the pathologist or lack of it".

Stewart who wrote the first edition of the Armed Forces Institute of Pathology Tumour Fascicle on Breast published in 1950 [10], used the photomicrograph of papillary intraductal carcinoma from the 1945 paper and added four other illustrations diagnosed as papillary cancer. In the legend of figure 17 in Stewart book, the term in situ ductal carcinoma "DCIS" was used for the first time. The statement regarding occult distinction and faith was reiterated.

In the first edition, 1953, of his classic textbook on surgical pathology [11] Ackerman illustrated comedocarcinoma as well as a true papillary carcinoma with fibrovascular stalks. During the 1950s and 1960s, he was skeptic about the malignancy of intraductal lesions other than the ones that he illustrated.

Pathology of DCIS

These tumours of the ductal system are wholly confined within the basement membrane. They result from a disruption in the architecture of the breast glandular epithelium involving loss of the hollow lumen and epithelial cell proliferation in acinar units that occurs via an imbalance between apoptosis and proliferation [12]. In the last several decades, the incidence of DCIS was raised from 5% to 20% of breast cancer [13, 14].

Multicentric foci are present in about a third of cases and in about 10% the lesion is bilateral and 2% are associated with Paget's disease of the breast [15]. Risk factors for invasive DCIS are similar to those for invasive carcinoma [13, 16, 17, 18, 19, 20, 21, 22 23, 24, 25, 26, 27].

Ductal carcinoma in situ comprises several histological types; solid, cribriform, papillary, micropapillary and comedo. This histological classification does not take into account important prognostic features such as nuclear grade "high, intermediate or low", necrosis "presence or absence" and polarization "architectural differentiation" [28, 29]. Recently a number of classification systems have been proposed to standardize the diagnosis of DCIS "Table 1". Almost all of them are based on the Bloom Richardson nuclear grading system. The cytological grading is advantageous over the histological grading because it offers a clue to the prognosis and clinical behaviour. Moreover more than one histological type can coexist in the same tumour.

Solid DCIS:

The duct is filled and distended with uniform medium sized cells. This uniformity of cell population, cytoplasm pallor and sharply outlined cell border are important diagnostic clues. The solid type of DCIS possesses the least propensity for evolving into invasive carcinoma [30]. Differential diagnosis includes ordinary hyperplasia, florid ductal hyperplasia & atypical ductal hyperplasia. {Figures 1, 2, 3 & 4}

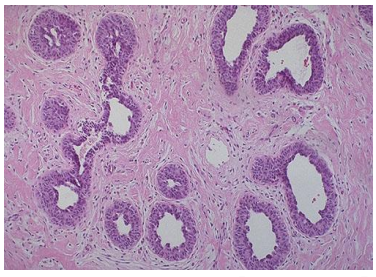

Figure .1. Normal Hyperplasia

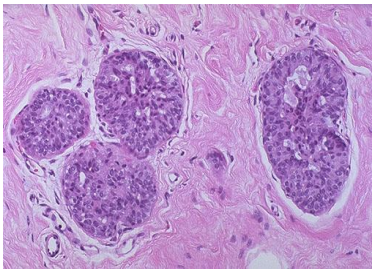

Figure .2. Florid epithelial hyperplasia

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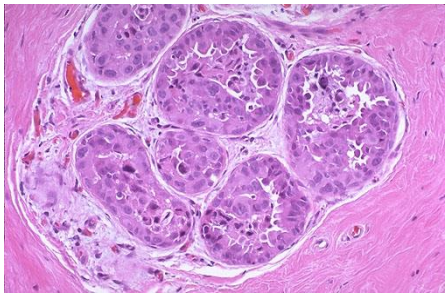

Figure .3.Atypical ductal hyperplasia

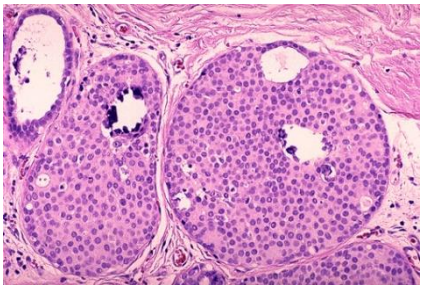

Figure .4.Solid DCIS

Comedo DCIS:

This is the most common histological type of DCIS. Cytologically it is more anaplastic than the other subtypes. The central mass of cells degenerates and the bulk of the lumen becomes occupied by an amorphous mass of cell debris. This necrotic core can be expressed from large ducts in fresh specimens. Diagnosis is easy and no other lesion mimics this type of DCIS. {Figure 5}

Cribriform DCIS:

The tumour cells are oriented into gland like formation with round lumina lined by rounded, cubical or columnar cancer cells and often containing a homogenous coagulum of secretion. The gland like spaces are more regular in shape more clearly delineated than in epitheliosis [17]. {Figure 6}

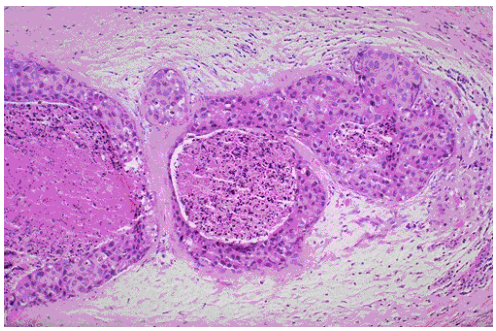

Figure .5. Comedo DCIS

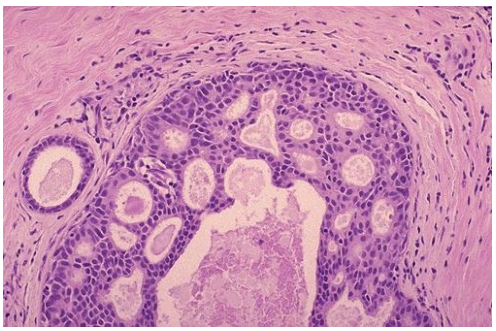

Figure .6. Cribriform DCIS

Micropapillary DCIS:

Dilated ducts with fingerlike papillary formation into the dilated lumina.

Papillary DCIS:

Large papillary formation with fibrovascular stalks. This is the malignant counterpart of the intraduct papilloma. {Figure 7}. It is a rare form that occurs in old age group. Clinically papillary carcinoma and papilloma have similar features [17]. Most commonly it arises de novo, but rarely can it arise within the context of multiple papilloma [31]. Sometimes it is very difficult to differentiate between papillary DCIS and ductal papilloma. Features fovaouring carcinoma are; uniformity in size and shape of the epithelial cells, presence of one cell type and lack of myoepithleial cells, nuclear hyperchromasia, high nuclear cytoplasmic ratio, high mitotic activity, lack of apocrine metaplasia, cribriform and trabecular patterns, scanty or absent stroma and lack of benign prolifeative disease in the adjacent breast. {Figure 7}

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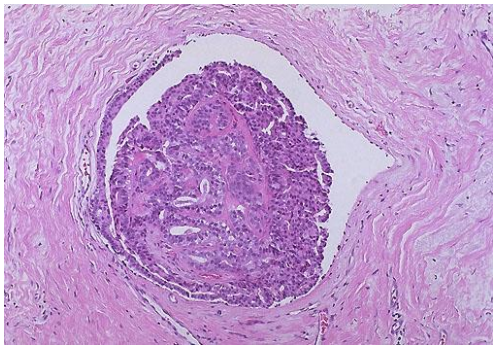

Figure .7. Intra ductal papilloma

Evolution of DCIS:

Intraductal epithelial proliferations of the breast are at present classified into three groups; usual epithelial hyperplasia, atypical ductal hyperplasia "ADH" and DCIS[43, 44]. Studies suggested the transition from normal epithelia via hyperplasia and atypical hyperplasia to ductal carcinoma [43, 45]. {Figures 8 and 9}. Invasion does not occur in all cases and when it does so usually it takes years, the risk being directly proportional to the degree of cytological atypia [46]. However, there are no clinical, morphological or biological indicators that sort out for sure those who will develop invasive cancer and no single factor so far seems to be particularly powerful in predicting progression [43]. Two interesting phenomenon might be encountered in the course of evolution of DCIS to IDC.

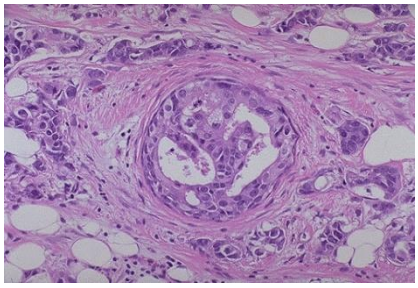

Figure .8: DCIS + IDC

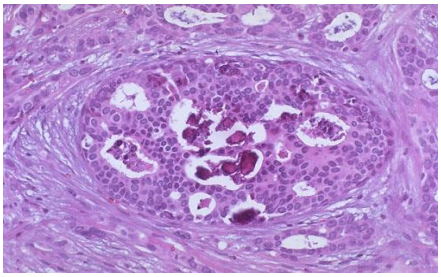

Figure.9. IDC + DCIS + Microcalcification

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Table 1

Author and Reference	Histological Variable	DCIS categories
Lagios[32].	Nuclear grade, architecture and necrosis.	High , intermediate and low grade
Ottensen[33].	Histological growth pattern, size of lesion, comedonecrosis and subhistological type.	Microfocal, diffuse and tumour forming
Bellamy[34].	Histological pattern, nuclear grade, necrosis and involved duct counts.	Comedo, solid, cribriform and micropapillary. All with nuclear grade.
Poller[35].	Architecture	Comedo, DCIS with necrosis and DCIS without necrosis.
Holland[36].	Cytonuclear differentiation, architectural and cell polarization.	Poorly differentiated, intermediately and well differentiated.
European breast screen group[37].	Cytonuclear differentiation	Poorly differentiated, intermediately & well differentiated.
Page[38, 39].	Architecture, nuclear grade and necrosis.	Low, intermediate and high grade.
Silverstein and Van Nuys[40].	Nuclear grade, comedo type and necrosis.	Group 1: Non high grade without necrosis. Group 2: Non high grade with necrosis. Group 3: High grade.
Consensus Committee[29].	Architecture, polarization, necrosis and nuclear grade.	Low, intermediate and high grade
Tavassoli[41].	Intraductal hyperplasia “IDH” and atypical ductal hyperpalais “ADH”.	Ductal intraepithelial neoplasia “DIN” Grade 1, 2 or 3.
Warnberg[42].	Histological grade, necrosis, lymphoid infiltration, mitosis, C-erb, P53, progesterone receptor, Bcl-2	Phenotype A and B

1. Microinvasion:

Microinvasion is the forerunner of invasive ductal carcinoma. It is defined as predominently non-invasive tumours in which there are one or more foci of infiltration, none measuring more than 1 mm in maximum diameter [47]. DCIS with Microinvasion “DCISM” constitutes 0.68 – 2.4% of breast cancer and 14% of DCIS [48, 49]. The potential for DCISM should be suspected in comedo type, large size tumour and tumours with necrosis [50, 51 and 52]. Recognition of stromal micro invasion can be extremely difficult. The occurrence of stromal granulomatous reaction, though rare, may be a useful indicator of micro invasion in breast cancer [53].

2. Intraepithelial spread:

Less commonly the malignant cells of DCIS, instead of penetrating the basement membrane to evolute into IDC, they spread intraepithelially either upward the duct towards the nipple to give rise to Paget’s disease of the breast or grow downward into the lobules to give rise to the so called cancerisation of the lobules. {Figure 10}

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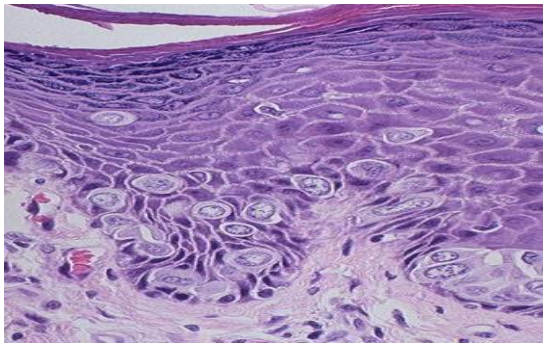

Figure .10: Paget's disease of the breast

Page et al [54] provided a 24 yr follow up data for a cohort of 28 women with non comedo small DCIS who had been discovered as an incidental finding and not as a palpable mass. They received no therapy other than a surgical excision. Breast cancer developed in 10 out of 28 patients. 9 out of the 10 were invasive. 7 out of them developed the cancer within 10 yrs.

Lagios et al [55] reported 79 patients with clinically occult DCIS measuring less than 25 mm treated by excision alone. With a mean follow up of 124 months, 13 patients developed recurrence "16%". The recurrence was 33% for high grade DCIS compared to 2% for patients with intermediate & low grades DCIS.

Bestill et al [56] from the Memorial Hospital in New York identified 25 cases with low grade papillary DCIS treated by excision alone. After a mean follow up of 21 yrs, 7 of 10 evaluable cases developed carcinoma, 6 of them were invasive.

Solin et al [57] reported 172 patients treated with excision plus irradiation and followed for a median of 78 months. He observed that local recurrence in patients with grade III DCIS and comedo DCIS occurred earlier "38 months" than in other patients "78 months".

Silverstein et al [50] reported an 11% incidence of local recurrence in women with comedo DCIS compared with 2% in non comedo DCIS in 96 females followed up for 45 months.

Current studies:

Several studies have addressed the prevalence of DCIS in the population. Kramer and Rush found that 6% of females above 70 yrs of age had DCIS & in half of the cases it is bilateral [58]. Alpers and Welling [59] found an incidence of 9%. Nielsen et al [60] study on autopsies "20 – 54 yrs age" found an incidence of 14%. Less than half of them were mammographically detectable. Howard et al [61] found a 10% false negative rate for DCIS which compares with the well known false negative rate of 15% for invasive carcinoma.

A recent study was conducted by Rosai [62]. He selected 5 pathologists with special interest in pathology of the breast and sent the same 17 tissue slides to each of them. A small area was circled in ink, which assured that each pathologist diagnosed precisely the same field of a non-invasive epithelial proliferation. The diagnostic choices were limited to usual hyperplasia, atypical hyperplasia or carcinoma in situ. In none of the cases was there agreement by all pathologists. In only 3 cases did 4 of the pathologists agree and in only 9 cases did 3 out of 5 agree. Moreover 6 cases had diagnoses that spanned the spectrum of usual hyperplasia, atypical hyperplasia and carcinoma in situ.

Schmitt et al [63] organised a similar study using 24 tissue slides of ductal proliferation. Before looking at the slides the six participating pathologists "3 of them participated in Rosai study" were given narrative and diagrammatic information regarding Page's criteria. Page circulated in tissue slides that he had diagnosed as usual hyperplasia, atypical hyperplasia or non comedo DCIS for review. After this preparation the study slides were sent out. All six pathologists agreed in 17 cases, and 4 of 6 pathologists agreed in 22 cases. The majority of discrepancies were between atypical hyperplasia and DCIS. Only two cases covered the spectrum of the 3 choices.

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The fundamental problem regarding DCIS is the diagnosis of the non comedo types with low nuclear grade. Are there any aids beyond the H/E sections? Lodato et al [64] showed a strong membrane staining against C-erb B-2 in 10 out of 10 comedo DCIS, but only 1 out of 14 small cell micropapillary cribriform cases and it stained weakly. Bartkova et al [65] correlated C-erb B-2 protein positivity in different types of DCIS with nuclear cell size. Almost all of the comedo DCIS had large size ">20 microM" nuclei, whereas all of the cribriform, papillary & micropapillary DCIS had less than 10 microM in diameter. All of the comedos had positive staining, whereas none of the non comedos stained. Unfortunately, the use of these kinetic techniques & oncogens abnormalities does not help when help is needed the most.

Till a sharp approach for the differential diagnosis of DCIS & epithelial hyperplasia show up & occult distinction between benign & malignant colours black & white, it is the duty of the unfortunate pathologist to make a distinction.

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